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10/830,190	04/21/2004	Ananth Annapragada	27428-4	7714

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

TH

Office Action Summary	Application No.	Applicant(s)	
	10/830,190	ANNAPRAGADA ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *15-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 25-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/31/04, 8/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 1-33 are pending in the application.

2. Applicant's election with traverse of Group IV in the reply filed on 4/5/07 is acknowledged. The traversal is on the ground(s) that groups I and IV are directed towards a composition comprising a sterically stabilized liposome and a nonradioactive contrast enhancing agent where the liposomes of group I specifically require a PEGylated liposome and group IV does not exclude PEGylated liposomes. This is found to be persuasive and groups I and IV are rejoined and examined.

3. Claims 15-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected groups II and III, their being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/5/07.

4. The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 33 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention. The claim language of the instant claim 33, such as the mol % ranges for the first lipid, second lipid and cholesterol, "58 to about 59 mol%, 5 to about 6 mol %, and 36-37 mol %", respectively were not found in the disclosure.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not adequately describe what constitutes, "a suspension medium that is essentially free of contrast enhancing agent" and therefore it is unclear and indefinite.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-10,12-14 and 25-32 are rejected under 35 U.S.C. 102(a) as being anticipated by Kao et al. *(Acad. Radiol.* **2003**, *10*, 475-483).

11. Kao et al. *(Acad. Radiol.* **2003**, *10*, 475-483) teaches of a CT liposomal iohexol formulation, for blood pool imaging, containing 34.8 mg iodine per ml and have an average diameter of 100.6 nm (p478, Liposomal iohexol formulation). An intravenous does of 475 mg I/kg provided a contrast enhancement of 130 HU and contrast enhancement was maintained for 3 hours after injection.(abstract). The liposomal formulations of the disclosure contain DPPC, cholesterol, DSPE-MPEG2000 in a 55:40:5 molar ration and iohexol. The liposomes were prepared without autoclaving and were dialyzed to remove the free iohexol from the suspension medium (p476, Liposomal iohexol formulations). The contrast enhancement is maintained for 3.5 hours after the last injection of contrast agent (p477, paragraph 4). The inclusion of the PEG into the liposomal membrane, created sterically stabilized liposomes which also helps avoid sequestration of the liposomes by the reticuloendothelial system (p481, paragraph 1).

12. Claims 1,3-7,9,10,12-14,25,26 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Klaveness et al. (US 5,676,928).

13. Klaveness et al. (US 5,676,928) teaches of an iodinated liposomal contrast enhancing composition comprising a neutral lipid (DPPC, column 7, line 18) and a charged lipid membrane, one of which may be derivatized with a PEG polymer to increase the circulation half-life, suspended in an aqueous medium (column 4, lines 8-26; column 11, lines 7-11). The iodinated X-ray contrast agents have an average particle diameter of the liposome is in the range of 50-3000 nm, 150-1000 nm or 200-

500 nm, a concentration in the range of 40-450 mg (column 4, lines 44-46 and 60+; column 9, lines 28-30) and be prepared by mixing, shaking, stirring, lyophilization and spray-drying without autoclaving (column 8, lines 46-55). In regards to stabilizing the liposomal composition, a stabilizing agent such as EDTANa_2Ca and TRIS buffer can be added (column 10, lines 23-24). The administration into the blood stream is usually intravenous administration (column 4, line 65) and with doses of 75 and 100 mg encapsulated iodine/X-ray attenuations of 47 and 70 HU respectively are observed (example 20).

14. Claims 1-4,7-10,12-14,25 and 27-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Sachse et al. (*Invest. Radiol.***1997**, *32*, 44-50).

15. Sachse et al. (*Invest. Radiol.***1997**, *32*, 44-50; pages provided are numbered 1-8) teaches of Iopromide-containing liposomes for enhancing CT imaging. The liposomes contain soy phosphatidylcholine (SPC), cholesterol, soy phosphatidylglycerol (SPG) (6:3:1 molar ratio) and 5 mol% DPSE-PEG2000 which are administered intravenously into a rat tail vein at a dose of 250mg I/kg (p3, paragraph 4) and show prolonged blood circulation with CT density differences above 70 HU (abstract; p2, paragraph 1). The CT blood pool imaging in a rabbit with DSPE-PEG liposomes show approximately 71ΔHU after 45 min (p5, paragraph 4; fig 6A-6D). Sachse et al. also discloses that the PEGylated lipid derivatives in the liposome membrane provides for potent increase in circulation times (p1, paragraph 2) as they avoid the mononuclear phagocytic system (MPS) and target to non-MPS organs.

16. Claims 1,3-8,10,14,25 and 28-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Tournier et al. (US 6,217,849B1).

17. Tournier et al. (US 6,217,849B1) teaches of an injectable iodinated liposomal composition sufficiently stabilized to carry an X-ray opacifying agent (column 6, lines 33-35) and allow convenient imaging of the blood stream via direct injection (column 3, lines 58+; column 4, line 37). The liposome comprise a first and second phospholipids, one whose phosphatidyl moiety is linked to glycerol, one bound to PEG, cholesterol additive and a carrier devoid of non-encapsulated contrast agent (column 4, lines 5 and 20-26; column 9, lines 24-25; column 13, lines 5-6). The injected dose of the liposomal contrast agent is 50-100 mg I/kg and the size of the vesicle may be 100nm (column 7, lines 36-44). The liposomal compositions of the disclosure may be administered intravenously to a subject (claim 4), are advantageous as they amount of iodine still in circulation one hour after injection can be as high as 50% of the injected dose which allows for satisfactorily imaging the blood pool (column 8, lines 55-60) and they are sufficiently stabilized to remain in the circulation for prolonged periods of time (column 5, lines 6-13).

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 1-4,7-14,25 and 27-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leike et al. (*Invest. Radiol.* **2001**, *36*, 303-308) in view of Torchilin et al. (*Biochim. Biophys. Acta* **1996**, *1279,* 75-83) or Sachse et al. (*Invest. Radiol.***1997**, *32*, 44-50).

20. Leike et al. (*Invest. Radiol.* **2001**, *36*, 303-308) discloses a computed tomography enhancing iodinated liposome composition containing soy phosphatidylcholine (SPC), cholesterol and soy phosphatidylglycerol (SPG) (p303, last paragraph). The contrast enhancing liposomal agents have a mean diameter of 201 nm are used for prolonged blood-pool opacification upon intravenous injection of 300mg I/kg (p305, paragraphs 3 and 8; p306, fig 2) which encompass the compositions for enhancing contrast of the instant claims. The contrast enhancing iodinated liposome compositions of the disclosure are observed immediately after administration up to 60 min with a mean peak enhancement of in the aorta of approximately 90ΔHU (p305, last paragraph; p306, first paragraph). Leike et al. does not disclose sterically stabilized PEGylated liposomes or targeted liposomes.

21. Torchilin et al. (*Biochim. Biophys. Acta* **1996**, *1279,* 75-83) discloses a PEG and/or antibody substituted liposome which are long-circulating and target-specific (p76, paragraphs 2 and 3). The blood circulation time of the liposomes are improved by coating the surface with PEG by decreasing their opsonization and recognition by the liver (p76, paragraph 2). The targeting of liposomes to infracted myocardium is possible since normal myocardial cells do not permit extracellular macromolecules, such as

antimyosin antibody, to traverse the cell membrane but necrotic cardiomyocytes with disrupted membranes cannot prevent the antibody from interacting with myosin (p76, paragraph 1). The liposomes are prepared by mixing PC, cholesterol and a PEG-PE (p77, paragraph 3).

22. Sachse et al. (*Invest. Radiol.***1997**, *32*, 44-50) teaches of lopromide-containing liposomes for enhancing CT imaging. The liposomes contain soy phosphatidylcholine (SPC), cholesterol, soy phosphatidylglycerol (SPG) (6:3:1 molar ratio) and 5 mol% DPSE-PEG2000 which are administered intravenously into a rat tail vein at a dose of 250mg I/kg (p3, paragraph 4) and show prolonged blood circulation with CT density differences above 70 HU as well as that stated above.

23. At the time of the invention it would have been obvious to one ordinarily skilled in the art to PEGylate liposomes for CT imaging of the vasculature as the blood circulation time of the liposomes are improved by coating the surface with PEG by decreasing their opsonization and recognition by the liver Torchilin et al. Generation of a long-circulating and target-specific liposome allows for site-selective administration of a CT liposomal composition directly to the site of interest to be imaged. One would have a reasonable expectation of success for substitute the liposomal membrane of any of the disclosures with a targeting antibody as the combination of disclosures provide for phospholipid formulations with increased blood circulation times. The increased liposomal circulation time allows for the antimyosin-modifies PEG-liposomes to circulate long enough to provide high target accumulation at the recognized target-binding site (Tochilin et al. p76, paragraph 2). Therefore it is advantageous to bind a targeting agent to a liposomal

membrane which provides increased blood circulation times for increased accumulation of the contrast agents to an infarcted myocardium and thus visualization of the infarcted myocardium.

24. Claims 1-14 and 25-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness et al. (US 5,676,928) or Tournier et al. (US 6,217,849B1) or Kao et al. *(Acad. Radiol.* **2003**, *10*, 475-483) in view of Torchilin et al. (*Biochim. Biophys. Acta* **1996**, *1279,* 75-83).

25. Klaveness et al. (US 5,676,928 in regards to claims 1-7,9-14,25,26 and 30) teaches of an iodinated liposomal contrast enhancing composition comprising a neutral lipid (DPPC, column 7, line 18) and a charged lipid membrane, one of which may be derivatized with a PEG polymer to increase the circulation half-life, suspended in an aqueous medium as well as that stated above. Klaveness et al. does not disclose a targeted liposome.

26. Tournier et al. (US 6,217,849B1 in regards to claims 1,3-8,10,11,14,25 and 28-31) teaches of an injectable iodinated liposomal composition sufficiently stabilized to carry an X-ray opacifying agent (column 6, lines 33-35) and allow convenient imaging of the blood stream via direct injection as well as that stated above. Tournier et al. does not disclose a targeted liposome.

27. Kao et al. *(Acad. Radiol.* **2003**, *10*, 475-483 in regards to claims 1-14 and 25-32) teaches of a CT liposomal iohexol formulation, for blood pool imaging, containing 34.8 mg iodine per ml and have an average diameter of 100.6 nm (p478, Liposomal iohexol

formulation). An intravenous does of 475 mg I/kg provided a contrast enhancement of 130 HU and contrast enhancement was maintained for 3 hours after injection as well as that stated above. Kao et al. does not disclose a targeted liposome.

28. Torchilin et al. (*Biochim. Biophys. Acta* **1996**, *1279,* 75-83) discloses a PEG and/or antibody substituted liposome which are long-circulating and target-specific (p76, paragraphs 2 and 3). The blood circulation time of the liposomes are improved by coating the surface with PEG by decreasing their opsonization and recognition by the liver (p76, paragraph 2). The targeting of liposomes to infarcted myocardium is possible since normal myocardial cells do not permit extracellular macromolecules, such as antimyosin antibody, to traverse the cell membrane but necrotic cardiomyocytes with disrupted membranes cannot prevent the antibody from interacting with myosin (p76, paragraph 1). The liposomes are prepared by mixing PC, cholesterol and a PEG-PE (p77, paragraph 3).

29. At the time of the invention it would have been obvious to one ordinarily skilled in the art to generate a long-circulating and target-specific liposome to allow for site-selective administration of a CT liposomal composition directly to the site of interest to be imaged. One would have a reasonable expectation of success for substitute the liposomal membrane of any of the disclosures of Klaveness et al., Tournier et al. or Kao et al. with a targeting antibody as all of the disclosures contain phospholipid formulations with increased blood circulation times. The increased liposomal circulation time allows for the antimyosin-modifies PEG-liposomes to circulate long enough to provide high target accumulation at the recognized target-binding site (Tochilin et al.

p76, paragraph 2). Therefore it is advantageous to bind a targeting agent to a liposomal membrane which provides increased blood circulation times for increased accumulation of the contrast agents to an infarcted myocardium and thus visualization of the infarcted myocardium.

Double Patenting

30. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

31. Claims 1-10 and 12-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3,8-13 and 17 of copending Application No. 11/595,808. Although the conflicting claims are not identical, they are not patentably distinct from each other because the composition for enhancing the contrast via X-ray of 11/595,808 encompasses the composition for

enhancing contrast via x-ray of the instant claims which are also capable of being administered intravenously into the blood stream. The composition of 11/595,808 contains an iodine concentration of about 37-200 mg I/mL which anticipates the concentration of at least 30 mg I/mL of the instant claims. Both compositions contain PEGylated liposomes that are sterically stabilized and have an average diameter of less than about 150 or 120 nm. The composition for use in computed tomography of 11/595,808 containing PEGylated liposomes provides a contrast enhancement of at least 50 HU for at least 30 minutes after administration as does the PEGylated liposomal composition for use in computed tomography of the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

32. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

33. Claims 25-33 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 27-35 of copending Application No. 11/568,936. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
April 17, 2007

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER